REMARKS

Claims 2-8, 10-16 and 36-40 presently appear in this case. No claims have been allowed. The official action of November 16, 2004, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for activating natural killer cells in a human patient by administering an effective amount of an adenosine A3 receptor agonist (A3RAg). The agonist will activate the NK cells by fully or partially activating the adenosine A3 receptors on the NK cells. This method may be used to treat diseases that are sensitive to activated NK cells, such as the treatment of malignant and infectious diseases. The process may include a step of determining that the disease or disorder is one that may be ameliorated through activation of NK cells.

Claims 1-16 have been rejected under 35 U.S.C. §102(b) as being anticipated by Jacobsen. The examiner states that Jacobsen discloses compounds that have been found to be selective A_3 adenosine receptor agonists, which overlap with the compounds of the present invention. The examiner states that the disease states and conditions that may be chronically treated include inflammatory disorders, Parkinson's disease, cardiac disease, and contraception. The examiner recognizes that Jacobsen is silent as to the activation of natural killer

cells, but the examiner states that those of ordinary skill in the art need not recognize the inherent characteristics or functioning of the prior art. This rejection is respectfully traversed.

Claims 1 and 9 have now been deleted in favor of new claims 39 and 40 that distinguish over the processes of Jacobsen. Claim 39 requires a step of determining that the disease or disorder is one that may be ameliorated through activation of NK cells. The examiner has conceded that Jacobsen teaches nothing about activation of natural killer cells. Accordingly, this determining step is not anticipated by Jacobsen, and would not have been obvious therefrom. Support for this step is inherent in the disclosure in the paragraph bridging pages 4 and 5 of the specification.

Claim 40 is distinguished from the disclosure of Jacobsen, as it requires that the disease be a malignant or infectious disease, and such are not among the diseases disclosed by Jacobsen in columns 25 and 26, as the examiner has acknowledged by not including claims 36 and 37 in this rejection. Accordingly, claim 40 and all of those claims dependent therefrom are clearly free of anticipation by Jacobsen. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 9-16 and 36-38 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Jacobsen in combination with Yao and Wansbrough. The examiner states that Jacobsen discloses compounds that have been found to be selective A_3 adenosine receptor agonists, such as IB-MECA. The examiner states that one skilled in the art will recognize that dosage will depend upon a variety of factors and that there are a wide variety of suitable formulations. The examiner notes that Jacobsen is silent as to the activation of natural killer cells, but it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared with the prior art disclosure. The examiner recognizes that Jacobsen differs from the instantly claimed invention in that Jacobsen does not teach the administration of A_3 receptor agonists to patients having a disease associated with malignant cells or a disease associated with cells infected with viruses, bacteria or protozoa. The examiner says that Yao teaches that A_3 agonists, such as IB-MECA, by virtue of regulating programmed cell death, may have application in treating diseases either in which cytotoxicity is undesirable, such as neurodegeneration, or desirable, such as cancer and inflammation. The examiner states that Wansbrough teaches the association of viruses and breast cancer. The examiner considers that it would have been

obvious to treat a patient having a disease associated with malignant cells by administering IB-MECA since Yao teaches the usefulness of both agonists for the treatment of cancer, as well as inflammation, as it was known in the art that there was a link between cancer and viruses. This rejection is respectfully traversed.

Yao teaches that A_3 agonists at high concentrations induce apoptotic cell death, for example in lymphoma cell lines, and, therefore, may have application in treating cancer. The present claims specify that the amount of A_3RAg administered is "an amount effective for fully or partially activating adenosine A_3 receptors on said NK cells, thereby activating said NK cells". The examples in the present specification establish that this activating amount is in the nanomolar (nM) range. The concentrations used by Yao are in the micromolar range (μM) and accordingly would not activate but rather would kill the cells by inducing apoptosis. Note the abstract of Yao, where it states that low concentrations of Cl-IB-MECA (10 nM or 1 μM) protect it against antagonist-induced cell death, but at concentrations $\geq$ 10 μM, the agonist alone produced apoptosis in various cell lines. At such concentrations, A_3RAg induces apoptosis in all types of cells, normal as well as tumor cells.

Attached hereto is a copy of Kim et al, "p53-Independent induction of Fas and apoptosis in leukemic cells by adenosine derivative Cl-IB-MECA" Biochem Pharmacol 63(5):871-880 (2002). At page 877, left column, first three lines of the discussion, Kim states:

> It has been reported that A_3AR agonists induce cell death in leukemic and other cells [10-15], while the mechanisms remain unknown.

Kim investigated the apoptotic effect of high concentrations ($\geq$ 30 μM) of Cl-IB-MECA and concluded that it was not mediated through the A_3 adenosine receptor (see, for example, page 877, right column, lines 22-23: "Therefore, Cl-IB-MECA did not act through a PLC-coupled A_3AR"; page 878, left column, lines 2-3: "Therefore, a mechanism other than activation of adenosine receptors seems to be responsible"). Moreover, a number of publications have reported that the apoptotic effect of high concentrations (in the μM range) was seen also in normal cells (see Kim et al, page 877, left column, first two lines of the Discussion).

It follows from Kim and Yao that the apoptotic effect is not mediated through the A_3 adenosine receptor, i.e., it does not exert its prime effect through the A_3 receptor. Thus, it would not have been obvious to combine Yao with Jacobsen for the treatment of malignancies or viruses. Jacobsen requires the use of amounts that permit use as a

selective A_3 adenosine receptor agonist. Yao requires amounts great enough to cause an apoptotic effect, at which amount the agonist is no longer A_3R selective.

Wansbrough adds nothing to the deficiencies of Jacobsen and Yao, i.e., the distinctly different dosages required for A_3R selective activity, as required by Jacobsen on the one hand, and apoptotic activity as required by Yao on the other hand. Furthermore, cancer is clearly not an infectious disease. Wansbrough would not suggest that any treatment that is useful for the treatment of cancer would be useful for the treatment of an infectious disease.

In summary, the present claims call for administration of an amount of A_3RAg effective for fully or partially activating adenosine A_3 receptors on NK cells. Those of ordinary skill in the art are well aware that adenosine receptor activation takes place at nanomolar concentrations and that at much higher concentrations, i.e., μM, A_3ARg agonists, such as Cl-IB-MECA are apoptotic. If they induce apoptosis in the natural killer cells, there will be no positive effect. Furthermore, because of the substantial differences between mechanisms and the amounts necessary to achieve such mechanisms in Jacobsen and Yao, it would not have been obvious to combine them, at the time the present

invention was made. For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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